Lung Screening Benefits and Challenges: A Review of The Data and Outline for Implementation

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ABSTRACT

Lung cancer is the leading cause of cancer-related deaths worldwide, accounting for almost a fifth of all cancer-related deaths. Annual computed tomographic lung cancer screening (CTLS) detects lung cancer at earlier stages and reduces lung cancer-related mortality among high-risk individuals. Many medical organizations, including the United States Preventive Services Task Force, recommend annual CTLS in high-risk populations. However, fewer than 5% of individuals worldwide at high-risk for lung cancer have undergone screening. In large part, this is due to delayed implementation of CTLS in many countries throughout the world. Factors contributing to low uptake in countries with longstanding CTLS endorsement, such as the United States, include lack of patient and clinician awareness of current recommendations in favor of CTLS as well as clinician concerns about CTLS-related radiation exposure, false-positive results, over-diagnosis, and cost. This review of the literature serves to address these concerns by evaluating the potential risks and benefits of CTLS. Review of key components of a lung screening program, along with an updated shared decision aid, provide guidance for program development and optimization. Review of studies evaluating the population considered "high-risk" is included as this may impact future guidelines within the United States (U.S.) and other countries considering lung screening implementation.

Keywords: Lung cancer screening, low dose CT, LDCT, CTLS

Introduction

Lung cancer is the leading cause of cancer-related deaths worldwide, accounting for 1.76 million deaths in 2018 (18% of all cancer-related deaths).[1] Every year, at least twice as many people die from lung cancer as from other common malignancies, including colorectal, stomach, liver and breast cancer.[1]

Approximately 8 million people in the United States (U.S.) alone are eligible for computed tomographic lung cancer screening (CTLS)[2], but in 2018 only 4% of eligible Americans were screened.[3] If all high risk individuals in the U.S. were screened, an estimated 48,000 lung cancer deaths could be prevented,[3] a number that exceeds the total number of lives lost due to breast cancer in the U.S. each year.[4] Lung cancer is also the most frequently fatal cancer In the European Union, causing more than 266,000 deaths yearly (21% of all cancer-related deaths).[5]

In this review of CTLS, we evaluate the potential risks and benefits in the current context, review perceived barriers to implementation, discuss key issues and components of successful screening programs, review risk models, and provide a shared-decision-making graphic for clinical use.

Lung Screening Trials: Examining the Evidence

Annual CTLS detects lung cancer at earlier stages than chest radiography (CXR) and leads to a reduction in lung cancer mortality in individuals at high-risk for the disease. First suggested by the International Early Lung Cancer Action Program (I-ELCAP)[6,7], a reduction in lung cancer mortality was confirmed by the National Lung Screening Trial (NLST), a U.S. multi-center, randomized controlled trial that enrolled >53,000 people and was halted early after detecting a significant 20% improvement in lung cancer mortality as well as a 6.7% improvement in overall mortality in individuals undergoing CTLS compared with those undergoing CXR.[8] The NLST evaluated CTLS at baseline and annually for the following 2 years without a defined algorithm to guide management of abnormal screens and was not designed to determine the degree of benefit achieved by a prolonged screening program. However, an extended analysis of the NLST showed that improvement in lung cancer specific mortality persisted up to 12.8 years.[9]

Since publication of the NLST in 2011, several other trials/analyses have assessed the impact of CLTS (the key characteristics and main findings of the trials are summarized in **Table 1**[8,10-26]). Later trials compared CTLS with standard of care (no screening; **Table 1**). The Dutch-Belgian Randomized Lung Cancer Screening Trial (NELSON) randomized high-risk individuals to CTLS versus observation. CTLS was performed at 0, 1, 3, and 5.5 years.[11] The trial involved more than 15,000 people aged 50–75 years with a high tobacco intake (≥15 cigarettes per day for ≥25 years or ≥10 cigarettes per day for ≥30 years; individuals who currently smoke or who quit ≤10 years prior).[11,12] Approximately 84%

were male.[11] In men, after 10 years of follow-up, the cumulative rate ratio for death due to lung cancer between the CTLS arm and the control arm was 0.76 (95% confidence interval [CI]: 0.61–0.94; *p* = 0.01), representing a 24% reduction in lung cancer-related death in the CTLS arm. In women, the reduction in lung cancer–specific mortality was much greater. The benefit in both sexes persisted at 11 years. Among screened male participants, lung cancers were stage I-II in 138 (68%) of 203 screen-detected lung cancers. In the same group, non-screen detected lung cancer were stage I-II in only 30 (21%) of 141 cases.[13] The non-screen-detected cases were diagnosed on imaging unrelated to the screening schedule, occurring either between scheduled screening studies or after the last scheduled negative screening study, at 5.5 years of the ten-year study. NLST reported similar trends; 70% of screen-detected lung cancer cases in the CTLS group were early stage, compared with 37% of non-screen-detected cases largely during follow-up after the 3 rounds of screening.[8] This suggests that ongoing regular screening, rather than years of follow-up without screening, would likely show an even greater difference in stage of diagnosis compared to the control arm with potential additional relative decrease in lung cancer mortality.

The Multi-centric Italian Lung Detection (MILD) study was conducted over 10 years and provided insight into the benefit of more prolonged consistent screening. This trial was initially designed to compare annual versus biennial CTLS, versus no intervention.[15] The results showed a 39% improvement in the risk of lung cancer-related mortality at 10 years in the two CTLS arms (pooled together), compared with the control arm (hazard ratio [HR]: 0.61; 95% CI: 0.39–0.95).[16] The magnitude of benefit increased when restricted to outcomes occurring after the 5th year of screening, leading to a 58% reduction in the risk of lung cancer-related mortality (HR: 0.42; 95% CI: 0.22–0.79).[16] When pooled with the MILD trial, the Detection And screening of early lung cancer with Novel imaging TEchnology (DANTE) trial showed a benefit in lung cancer overall mortality with CTLS, compared with no screening[27]; similar findings were also found in the Italian Lung Cancer Screening Trial (ITALUNG).[17] While the Danish Lung Cancer Screening Trial (DLCST) did not show a benefit of screening on lung cancer mortality versus the control arm, the results were calculated after only 5 years of follow-up with only 2000 subjects per arm, limiting the power of the study to detect a mortality benefit.[20] Finally, findings from the German Lung cancer Screening Intervention (LUSI) trial were in line with those from other trials, including the NLST and NELSON, suggesting a stronger reduction in lung cancer mortality after CTLS among women, compared with men.[26] The accumulation of data and experience with CTLS exceeds that of other routine cancer screenings and has led to important insights that further guide CTLS implementation and future studies for ongoing improvements.

Current Guidelines and Recommendations on CTLS

In December 2013, the United States Preventive Services Task Force (USPSTF) released their initial recommendation for lung screening.[28] Most U.S. programs conducting CTLS at that time had adopted either the NLST or National Comprehensive Cancer Network (NCCN) positive solid pulmonary nodule size thresholds of ≥4mm in maximum (NLST) or mean (NCCN) diameter. In 2014, the NCCN and Lung-RADS® increased the size threshold at which a solid pulmonary nodule would trigger a positive CTLS exam designation to ≥6mm in mean diameter, after research by multiple organizations demonstrated a significant increase in positive predictive value and a minimal increase in false negative exams at this larger threshold size.[29-33] In current clinical practice, analysis of the performance of CTLS should reflect this established positive size threshold when utilizing 2D measurements.

Many medical organizations recommend annual CTLS in populations at high risk of lung cancer. **Table 2**[32,34-48] summarizes published guidelines. While there are some minor variations between the definitions of 'high-risk', the criteria used are generally driven by age and smoking history.[8] More recent CTLS studies have included individuals with less tobacco exposure, and consequently, adjustment to the recommendations may follow. We review the topic of "high-risk" in another section. Guidelines are yet to be published in China, but thoughtful consideration specific to the population is underway.[49] Additional guidelines on CTLS are available, including the European Society for Medical Oncology (ESMO)[50], European Society of Thoracic Surgeons (ESTS)[51] recommendations, and the European position statement on lung cancer screening.[52]

Perceived Barriers to the Implementation of CTLS Screening for the Prevention of Lung Cancer

Following publication of the NLST,[8] guidelines in the U.S. were updated to recommend CTLS in a high-risk population. Despite these longstanding recommendations, rates of screening implementation and uptake in the U.S. have been limited.[53-56] A number of factors may contribute to the low uptake of CTLS (see **Table 3**), including a lack of patient and clinician awareness of the mortality benefit of CTLS, as well as clinician concerns about CTLS-related radiation exposure, false positive results, over-diagnosis and overtreatment, health system resources utilization and cost-effectiveness.[57-59] In addition, stigma against individuals who smoke and/or nihilism about lung cancer outcomes may bias both clinicians and patients.[60] Most often, cancer screening occurs after a discussion with a primary care provider (PCP), and patients cite their PCP's advice as important to their decision-making. It is therefore important for PCPs to understand the benefits and risks of CTLS and the appropriate screening criteria.[61] Lack of CLTS knowledge may prevent PCPs from engaging in

shared-decision making (SDM) conversations with their patients.[62] A recent study reported that PCPs who are less familiar with the qualifying CTLS criteria had 2.7 times higher odds of ordering CXR than CTLS.[62] The Centers for Medicare & Medicaid Services (CMS) requires the use of a formal decision-aid as part of CTLS SDM.[40] An accurate decision-aid that is understandable to the general public is critical, and we provide an updated decision-aid for use in clinics (**Fig. 1**[63,64]).

Although clinicians may have concerns about the level of radiation associated with CTLS, this risk appears minimal in the CTLS setting. According to the Health Physics Society, the risk of radiation in the diagnostic realm (<100 mSv) is either too low to measure or non-existent.[65] While current guidelines recommend a CT dose index ($CTDI_{vol}$) of ≤3 mGy for standard sized patients,[66] an achievable dose for CTLS in clinical practice is less than half of this level.[8] In addition, screening currently occurs in populations aged from 50/55 to 80 years in which any risk of radiation-induced cancer is significantly reduced. Clinicians should consult their local guidelines for further information on radiation exposure.[52,67]

The false positive rate of screening exams is a critical metric in assessing test effectiveness and should be part of every SDM discussion. The NLST reported that 24.2% of CTLS exams performed were positive for a nodule ≥4 mm in maximum diameter, resulting in a false-positive rate of 23.3%. Unfortunately, many subsequent publications describing the NLST results have misreported the 96.4% NLST false discovery rate (the percent of positive exams which are false positive) as the false positive rate.[8] A re-analysis of the NSLT using ≥6 mm mean diameter positive solid nodule size threshold yielded a significant decrease in the false positive rate to about 13% at baseline and 5% for subsequent annual screening exams,[68] which is similar to the false-positive rate of mammography.[69,70] In many cases, a positive CTLS exam is followed by a repeat scan in 3–6 months; if stable, this interval follow-up exam will be considered negative, and an annual CTLS exam will be performed 12 months later.[32] The NELSON protocol reported fewer false positives by including an "indeterminate" classification for certain nodules that required a repeat computed tomographic (CT) scan to monitor for changes in size before defining the final screening-test outcome[71] rather than classifying them as positive in the baseline exam. UK Lung Cancer Screening trial (UKLS) investigators suggest that making the distinction between findings that require CT follow-up from findings that require referral for consideration of more invasive workup may be meaningful for the patient's perspective.

Following standardized reporting algorithms such as I-ELCAP, NELSON, the NCCN protocol and Lung-RADS®, invasive procedures are limited to a subset of the most suspicious findings. It is important for all screening programs to utilize a standardized system to reduce the number of unnecessary interventions. Although low in numbers, resection of benign nodules does occur. It is important to

balance the risk of resecting benign nodules and watching suspected lung cancer progress without action.[72] Distinguishing benign or indolent nodules from malignant nodules is an important area of ongoing research.

Although over-diagnosis was regarded as a concern after initial NLST estimate of 18%, recent analyses have indicated that over-diagnosis (and therefore over-treatment) may not be a significant problem for CTLS. Follow-up data from the NLST showed that there was no significant difference in diagnosed lung cancer between the CTLS and chest radiography groups with follow-up periods up to 11 years.[9]

CTLS appears cost-effective in healthcare systems in which it was assessed and compares well with other routine cancer screenings, including colorectal, breast and cervical cancers.[73,74] An economic evaluation of the Manchester Lung Health Check pilot found that CTLS represents a cost-effective use of NHS resources.[75] The cancer detection rate (CDR) was ~3%, and the cost effectiveness ratio was ~£10,000 per Quality-Adjusted Life Year (QALY),[75] which is substantially less than the $81,000 per QALY calculated from the NLST.[74] These findings have been supported by cost data from CTLS trials.[76] For example, the PanCan screening study (Canada; CDR = 4% over 18 months) reported that treating lung cancer with curative surgery is more cost effective than treating late-stage lung cancer.[77]

Gender and socio-economic status may affect access to CTLS. A recent analysis showed that patients in CTLS programs tend to have relatively high socio-economic status and are mostly male,[78] highlighting the need for strategies that focus on better engaging women and people with low-economic status at high-risk for lung cancer.[78] In addition to limited access, some populations, including women and Black men, have a higher risk of lung cancer after adjusting for other risk factors including age and smoking exposure. Therefore, some individuals that fail to meet CTLS eligibility criteria carry a higher risk of lung cancer than those who qualify.[79] The perception of risk and concerns about developing lung cancer varies with age, race and health insurance status, which should be considered in efforts to improve participation rates.[80]

In the U.S., despite the proven effectiveness of CTLS, established reimbursement, and years of near universal support from governmental agencies and medical societies, uptake remains low. To increase CTLS utilization, widespread awareness and education campaigns are needed to improve clinician engagement. Educational interventions should focus on appropriate CTLS settings and eligibility criteria. Engaging underserved at-risk populations is important as CTLS programs are initiated, to avoid increasing the significant disparities that have been inherent within healthcare systems.

Key Issues and Components of Successful Lung Screening Programs

Implementation of a CTLS program requires several foundational elements[81] that cover the entire CTLS pathway, from identification of the target population to treatment and follow-up. This begins with accurate selection of the people at high risk for lung cancer who would benefit from CTLS (section 5). Essential core elements of a CTLS program include a program navigator and a reliable database for nodule/patient monitoring.[48,82] A multi-disciplinary steering committee facilitates the management of a program that involves multiple specialties. Other aspects for particular attention include the following.

1. Participation requires a robust system to identify individuals for CTLS and to track participants over years of follow-up. In the U.S., identification of individuals is generally accomplished by PCPs. The internal CTLS program infrastructure is of paramount importance to support PCPs and other ordering providers. Primary care representation on hospital CTLS steering committees is crucial to help identify workflow issues and system tools that may impact enrollment. Some more centralized health care systems around the world allow for systematized identification of individuals for CTLS. Attention to optimizing the involvement of all high-risk populations is of particular importance to prevent significant disparities. Smoking is increasingly concentrated in disadvantaged populations, including those living below the poverty level, those with disabilities and those experiencing psychosocial distress.[83] These populations often distrust the medical community and face structural challenges that reduce access to care. They often experience stigma and implicit bias, both as people who smoke and related to their disability, race/ethnicity and socioeconomic situation.[79] Partnering with community leaders and community health workers, along with developing empathetic, culturally appropriate outreach initiatives is essential to avoid exacerbating existing care access disparities. Some programs offer CTLS within a broader lung health-check framework. This may enhance participation because those involved feel that they are doing something positive about their health. It also reduces the focus on lung cancer, which may be alienating, and allows clinicians to capitalize on the clinic attendance by identifying and acting on unmet health needs.[81]

2. Shared decision-making (SDM) is an important component of any medical decision. In the U.S., formal SDM, including use of a decision aid, is required by CMS to order CTLS. This CMS requirement for SDM is unique to CTLS and a potential barrier to screening uptake if overly cumbersome or misrepresenting the balance of risks and benefits. We provide an updated decision aid (**Fig. 1**) for use in clinical practice and encourage clinicians to print this for practical use during SDM discussions in clinic. This decision aid provides the background to allow for more effective discussion of patient preferences, because it incorporates the full duration of screening eligibility (as opposed to a certain number screenings in a clinical trial setting). The components of the decision aid are organized to

guide counseling of patients on risks versus benefits of lung screening, starting with the likelihood of diagnosis of lung cancer and risk of an unnecessary invasive procedure. This is followed by the implications of early detection, staging, and mortality for those who develop lung cancer. The first aspect of SDM for patients to consider is the risk-benefit ratio of CTLS. In **Figure 1*A*** we outline the likelihood of diagnosis of lung cancer and the risk of an unnecessary invasive procedure from CTLS over the years of recommended screening. The likelihood of developing lung cancer in the CTLS eligible population may be as high as 10−16%.[84] Our decision aid conservatively estimates the risk at 10%. A 5-year survival chart (**Fig. 1*B***) and survival curves (0–72 months) by stage (**Fig. 1*C***) provide context for the graphic demonstrating stage of diagnosis within a CTLS program (**Fig. 1*D***) compared with diagnosis outside of a CTLS program (**Fig. 1*E***). The larger randomized studies on lung screening each incorporate a limited number of scans followed by years without scans, during which higher numbers of later stage lung cancer are diagnosed. Baseline scans also include a higher number of later stage diagnoses than the following yearly scans. The stage breakdown in the figure is a representation of the experience of the authors with mature lung screening programs. This decision aid will remain accurate after the USPSTF has finalized its updated lung screening recommendations, because the lung cancer risk ratio will not substantially change in a younger population with less smoking history (start age of 50, with at least 20 pack years[85]).

3. Standardized radiology reporting is important to ensure pathway management of findings. In the absence of a standardized reporting system, management of nodules can be inconsistent, leading to over-management of benign nodules and potential for delays in the diagnosis of suspicious findings. An understanding of the currently available classification systems is important for the development and management of screening guidelines, but excessive focus on the pros and cons of the different management systems may prove to be a barrier to implementation. In the U.S., nodule size and growth assessment relies on 2D measurements (**Table 1**), whereas in parts of Europe, semi-automatically measured volume and volume-doubling time may be the preferred approach.[52] It is undoubtable that reporting systems will evolve as CTLS understanding improves. Nevertheless, it is likely more important to follow an established guideline consistently than to delay implementation of a CTLS program due to concerns about which guideline to follow.

4. Care Escalation Pathways are required for all suspicious findings. Nodule clinics staffed by pulmonologists and/or thoracic surgeons, with significant input from radiology, are helpful and can reduce the burden on the ordering PCP, who may be less well-equipped to determine when biopsy or other intervention is indicated. Guidelines highlight when care escalation is recommended.[86,87] Various guidelines/reporting systems use different CTLS overall exam assessment terminology (e.g., reports of “indeterminate” exams in patients in the European NELSON trial correlate somewhat

with Lung-RADS 3 "positive" and certain Lung-RADS 4A "suspicious" findings in the most commonly used U.S. system). In either scenario, follow-up with a nodule specialist is critical for all "suspicious" findings to determine if intervention is indicated. The crucial consideration is the potential impact on the patient; an "indeterminate" Lung-RADS 3 classification generally implies a short interval repeat CTLS exam, whereas a "suspicious" classification implies the potential need for invasive interventions.

Based on our experience, reliable, standardized reporting systems should identify fewer than 8% of exams per round of CTLS that warrant care escalation. Reasonable efforts should be made to avoid intervention for non-malignant findings. An aggressive approach designed to eliminate delays in diagnosing lung cancer carries some risk of unnecessary intervention. A robust database for tracking nodules and outcomes can provide internal data necessary for individual clinicians and programs to monitor outcomes and rates of interventions for malignant or benign nodules. Like all types of clinical care, experience improves the process and the outcomes.

5. Significant Incidental findings lack a consensus definition. Widespread adoption of a standard definition would enhance the development of management guidelines. Some centers consider a "significant incidental finding" to be any new or unknown unexpected finding that warrants some form of clinical or imaging evaluation before the next scheduled CTLS exam. Emphysema and coronary artery calcifications (CAC) are highly prevalent in the CTLS-eligible population. In this regard, they are not unexpected and therefore are not classified as "significant incidental findings". Instead they are expected findings on CTLS exams that should be reported and managed accordingly. In contrast an unknown breast, renal or liver mass without benign radiographic features would qualify as a "significant incidental finding" requiring urgent targeted clinical/imaging assessment.

6. Smoking cessation counselling is an important aspect of CTLS. Higher levels of sustained quit rates have been noted in CTLS programs relative to the general smoking population.[88] CTLS provides multiple opportunities to counsel and provide advice on quitting for patients who smoke. Studies have shown that even a brief 3-minute intervention on cessation can increase quit rates.[89] In just one year of CTLS program enrollment there are up to 6 opportunities for smoking cessation advice/counseling.[90] In fact, one study of smoking cessation in a clinical CTLS program found that the longer a person was in a screening program the more likely they were to quit smoking.[91] Opportunities for increased smoking cessation rates in CTLS programs have additional benefits of improving health outcomes from other tobacco related diseases such as heart disease, chronic obstructive pulmonary disease (COPD) and many other cancers. Including smoking cessation in CTLS also improves the cost effectiveness of the program.[92]

Use of Risk Models

In recent years a number of risk-prediction models have been developed (**Table 4*A***[93-105] and ***B***[93,96,98-105]), with the aim of improving the selection of individuals for lung cancer screening. Compared with applying the eligibility criteria of the NLST trial, or related criteria such as those recommended by the USPSTF or CMS, risk prediction-modeling more accurately selects individuals at higher risk of lung cancer. These models may optimize screening outcomes, such as the number needed to screen to avoid one death.[103 22,106] Recently, the International Lung Screening Trial (ILST) initiative used both the $PLCO_{m2012}$ and USPSTF models as entry criteria in a screening program.[107] $PLCO_{m2012}$ alone identified 25% of cancers, while only 1.6% of cancers were found using USPSTF criteria.[107] Risk modelling is more granular when assessing individual risks, and can account for non-linear relationships to improve predictive accuracy. Additionally, the $PLCO_{m2012}$ risk model has been shown to reduce the disparity in eligibility for screening using age and tobacco history for Blacks as compared to Whites.[79] Risk models can be enhanced by including additional predictors, such as the patient's latest CTLS or biomarker results.[108,109] As technologies improve, deep learning algorithms may further enhance lung cancer screening.[110] However, many models are not practical for population-based CTLS, because they require blood or genetic tests, or extensive medical record data, or are limited to specific populations. There is a need for greater incorporation of prediction modeling into CTLS guidelines and programs.

Summary

Understanding of the risks and benefits of CTLS and important components of a successful CTLS program have evolved with increasing studies/trials and CTLS program experience. Some early assumptions and conclusions have persisted, and some have been misinterpreted and incorrectly reported. It is essential that comprehensive CTLS programs be implemented, rather than arising as a byproduct of sporadic ordering of scans by providers without a program infrastructure in place. Given the potential for such a large number of lives to be positively impacted by a timely diagnosis of early-stage treatable disease, the initiation of CTLS programs should be given the highest priority by healthcare institutions and providers.

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Table 1. Selected Lung Cancer Screening Studies

	NLST[8,10]	NELSON[11-14]	MILD[15,16]	ITALUNG[12,17-19]	DLCST[12,20,21]	UKLS[22,23]	DANTE[24,25]	LUSI[26]
Study design								
Randomized, Y/N	Y	Y	Y	Y	Y	Y	Y	Y
Screening interval, y	1	1; 2; 2.5	1 or 2 (rand)	1	1	0/0.25/1	1	1
Number of screens, n	3	4	5 annual/ 3 biennial	4	5	1[a]	5	5
Overall follow-up, y	7.4	10	10	8.5 (median)	10	10	8.35 (median)	8.8 (median)
Comparator	CXR	No screening	No screening	No screening	No screening	No screening	No screening	No screening
Inclusion criteria[d]								
Pack-years	≥30	≥15/d[b] for >25y OR >10/d[b] for >30y	≥20	≥20	≥20	NA[c]	≥20	≥15/d for V25y or ≥10/d for ≥30y
FS[i]: abstinence, y	≤15	<10	<10	<10	≤10 (age >50 y)	-	<10	<10
Age, y	55–74	50–75	49–75; no cancer in <5 y	55–69	50–70	50–75	Males, 60–74	-
Patients								
Total randomized, n	53,452[77]	13,195[e]	4099	3206	4104	4055	2450	4052
CTLS arm, n	26,722	6583[e]	2376	1613	2052	2028[f]	1264	2029
Age, y	61±5[g]	CTLS: 58 (55–63)[e,h] C: 58 (54–63)[e,h]	Intr: 58 C: 57 (NR)[h]	60.9±4[g]	57.9±5[g]	CTLS: 67.1±4.1 C: 66.9±4.1[g]	64 (5)[h]	CTLS: 55[h] C: 55[h]
Age range, y	55–74	CTLS: 46–76[e] C: 34–89[e]	49–75	55–69	50–70	50–75	60–74	50–69
Males, %[j]	59.0	100[e]	68.4/63.3	64.7	55.2	~75	100	CTLS: 50.1 C: 49.9
Smoking history								
Pack-years	48 (27)[h]	CTLS: 38 (30–50)[e,h] C: 38 (30–50)[e,h]	39/38 (NR)[h]	40 (NR)[h]	S: 36.4±13.4[g] C: 35.9±13.4	NR	45 (30)[h]	NR
Currently smoke, %	48.2	CTLS: 55.5[e] C: 54.8[e]	68.6/89.7	64.8	76.1	38.7	56.9	CTLS: 50.2 C: 49.8
Key outcomes								
Primary outcome	20% ↓ in LC-related mortality	24% ↓ in LC-related mortality (10 y)[e]	39% ↓ in LC-related mortality (10 y)	17% ↓ in LC-related mortality; 30% reduction in overall mortality	No statistically significant effect on LC-related mortality	LC prevalence 1.7% at baseline	No statistically significant effect on LC-related mortality	No statistically significant effect on LC-related mortality
Mortality, %								

General: CTLS/C	13.0/14.0[k]	13.9 / 13.76[e,k]	5.8/6.2	9.5/11.4	8.0/7.9	NR	14.2/14.8	HR: 0.99 (95% CI: 0.79–1.25) p = 0.95
Lung-cancer: CTLS/C	2.5/3.1[k]	2.5 / 3.3[k]	1.7/2.3	2.7/3.8	0.2/0.2	NR	4.7/4.6	HR: 0.74 (95% CI: 0.46–1.19) p = 0.21
Lung cancers detected, n CTLS/C	1701/ 1681[9]	203/304[13]	98/60[16]	67/71[17]	100/53[20]	42/NR[22]	104/72[25]	85/67[26]
Stage, n (%)								
Stage I: CTLS/C	673 (40)/ 462 (27)	119 (59)/ 41 (14)[e]	49 (50)/ 13 (22)	24 (36)/ 8 (11)	50 (50)/ 8 (15)	28 (67)/ NR	47 (45)/ 16 (22)	48 (57)/ 6 (9)
Stage II: CTLS/C	145 (9)/ 153 (9)	19 (9)/ 30 (10)[e]	4 (4)/ 5 (8)	5 (8)/ 5 (7)	4 (4)/ 2 (4)	8 (19)/ NR	7 (7)/ 5 (7)	7(8)/ 9(13)
Stage III: CTLS/C	298 (18)/ 321 (19)	33 (16)/ 77 (25)[e]	16 (16)/ 10 (17)	9 (13)/ 8 (11)	23 (23)/ 9 (17)	3 (7)/ NR	17 (16)/ 12 (17)	12 (14)/ 21 (31)
Stage IV: CTLS/C	468 (28)/ 597 (36)	19 (9)/ 139 (46)[e]	29 (30)/ 32 (53)	24 (36)/ 35 (49)	23 (23)/ 32 (60)	3 (7)/ NR	26 (25)/ 33 (46)	17 (20)/ 30 (45)
Unknown stage: CTLS/C	112 (7)/ 143 (9)	13 (6)/ 17(6)	0(−)/ 0(−)	5 (8)/ 15 (21)	0 (-)/ 2 (4)	0 (-)/ NR	7 (7)/ 6 (8)	1 (1)/ 1 (2)

[a]Repeated only if category 2 nodule or above detected in initial screen; [b]cigarettes per day; [c]Inclusion based on risk model (led to inclusion of two individuals who had never smoked); [d]DLCST also specified: FEV_1 at least 30% of predicted; Able to climb two flights of stairs (total of 36 steps) without pausing; [e]primary analysis (males only); [f]1994 underwent CT screening; [g]mean ± SD; [h]median (IQR); [i]people who used to smoke were also required to meet the pack-years criterion; [j]data shown are the average percentage between the treatment arms or the percentages for the treatment and control arms (as reported in each article); [k]deaths per 1000 person-years; [k]occult: CTLS = 5, C =4.

C, control; CI, confidence interval; CS, people who currently smoke; CT, computed tomographic; CTLS, computed tomographic lung screening; CXR, chest x-ray; DANTE, Detection And screening of early lung cancer with Novel imaging Technology; DLCST, Danish Lung Cancer Screening Trial; FS, people who used to smoke; HR, hazard ratio; IQR, interquartile range; ITALUNG, Italian Lung Cancer Screening Trial; LC, lung cancer; LUSI, German Lung cancer Screening Intervention; MILD, Multi-centric Italian Lung Detection; NELSON, Dutch-Belgian Randomized Lung Cancer Screening Trial; NLST, National Lung Screening Trial; NR, not reported; rand, randomized; SD, standard deviation; UKLS, UK lung cancer screening trial.

Table 2. Recommended Eligibility Criteria for CTLS in Patients at High Risk of LC

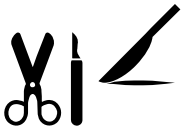
	Criteria for patients to be considered for CTLS				
Guideline	**Year**	**Age, y**	**Pack-years, y**	**Time since stopped smoking, y**	**Comments**
AAFP[34]	2013	Insufficient evidence			Eligibility criteria were based on one study (NLST); shared decision-making was recommended instead
AATS Tier 1[35]	2012	55-79			-
AATS Tier 2[35]	2012	50-79			Must have additional risk (≥5%) of developing lung cancer within 5 years (e.g., prior cancer, genetics)
AATS Tier 2 (alternative) [35]	2012	Any	Any/none	Any/none	Lung cancer survivors with no evidence of disease for 4 years
ACCP[36]	2018	55-77	≥30	≤15	Evidence-based smoking cessation treatments are recommended
ACS[37]	2013	55-74	≥30	≤15	'Apparently healthy'
ALA[38]	2020	55-80	≥30	≤15	-
ASCO/ATS[39]	2015	55-74	≥30	≤15	-
CMS[40]	2015	55-77	≥30	≤15	Offered to asymptomatic Medicare beneficiaries if they agree to receive counselling and participate in shared decision-making before screening
CCO[41,42]	2013	55-74	≥30	≤15	Patients must be 'disease-free' at time of screening
ESR/ERS[43]	2015	55-80	≥30	≤15	
Japanese Imaging Guidelines[44]	2013	≥50	-	-	Brinkman index ≥600
K-LUCAS (NCCK)[45]	2018	55-74	≥30	≤15	-
NCCN Cat 1[32]	2017	55-74	≥30	<15	-
NCCN Cat 2[32]	2017	≥50	≥20	-	Must have additional risk factor[a] Alternatively, consider those with ≥1.3% threshold of lung cancer over a 6-year timeframe, based upon the $PLCO_{m2012}$ model
French (SPLF, IFCT, SIT)[46]	2012	55–74	≥30	<15	Currently being revised. Likely to use NELSON entry criteria (50-75 y old; 10cig x 30y or 15cig x 25y; former <15y)
USPSTF[28]	2013	55-80	≥30	≤15	-

Table adapted from the ATS & ALA Lung screening implementation guide.[48]

[a]Cancer history, family history of lung cancer in first-degree relative, COPD or pulmonary fibrosis, radon exposure, occupational exposure.

AAFP, American Association of Family Physicians; AATS, American Association of Thoracic Surgery; ACCP, American College of Chest Physicians; ACS, American Cancer Society; ALA, American Lung Association; ASCO, American Society of Clinical Oncology; ATS, American Thoracic Society; Cig, cigarettes; CMS, Centers for Medicare & Medicaid Services; CCO, Cancer Care Ontario; COPD, chronic obstructive pulmonary disease; CTLS, computed tomographic lung screening; ERS, European Respiratory Society; ESR, European Society of Radiology; IFCT, The French Cooperative Thoracic Intergroup, K-LUCAS, Korean Lung Cancer Screening Project; LC, lung cancer; NCCN, National Comprehensive Cancer Network; NCCK, National Cancer Center, Korea; NELSON, Dutch-Belgian Randomized Lung Cancer Screening Trial; NLST, National Lung Screening Trial; SITC, Society for the Immunotherapy for Cancer; SPLF, Société de Pneumologie de Langue Française; USPSTF, United States Preventive Services Task Force.

Table 3. Common perceived Barriers to Lung Cancer Screening

Perceived barrier	Comments
Unwanted consequences of radiation exposure 	• Risk of radiation appears non-existent or too low to be measureable • No reported cases of radiation-induced malignancy
False-positive findings/overdiagnosis 	• False-positive findings occur less frequently than has been reported • 'False discovery' has been misinterpreted/misreported as 'false positive' • No difference in rates of diagnosis between CTLS and chest radiography groups; suggests that over-diagnosis is not a major concern
Unnecessary invasive procedures 	• Low numbers of resections of benign nodules • Need to consider balance between resection of benign nodules and watching lung cancer progress without action • Implementing a standardized system reduces the number of unnecessary interventions

CTLS, computed tomographic lung screening.

Table 4A. Selected Risk Prediction Models for Lung Cancer[a]

Model	Study Details		Validation (AUC)		Advantages/limitations
			Internal	External	
Bach[93]	USA; CHS; n = 18,172	45–69 y 20 pack-years, or quit in last 15 y	0.72[93]	Finland: 0.69[94] Massachusetts, USA: 0.66[95]	Only tested in high-risk CS/FS. Complicated data collection for asbestos exposure; may not be suitable for lung cancer screening programs
Liverpool Lung Project[96]	UK; C-CS; n = 1736	20–80 y	0.71[96]	Europe: 0.67; USA: 0.76; UK: 0.82[97] Massachusetts, USA: 0.69[95]	Evidence for accurate prediction in people who do not smoke is lacking. Calibration appears poor in areas where decision thresholds may lie[97]
Spitz[98]	Texas, USA C-CS; n = 3852	No restrictions[b]	Test: NS: 0.57; FS: 0.63; CS 0.58	Massachusetts, USA NS: 0.68; FS: 0.70; CS: 0.68[95]	Some variables used to match case-control data were strong predictors of lung cancer; this reduced the predictive ability of the model
African-American[99]	Houston, USA C-CS; n = 988	African-American	Development: 0.75 Test: 0.63		No external validations conducted outside of the original study
$PLCO_{m2012}$[100]	USA, 10 centers; CHS; n = 80,375	CS/F	Development: 0.803 Test: 0.797	Multiple true external validations, in countries where AUC is ~0.80	Included African Americans and indigenous Americans (at increased risk)
Hoggart[101]	Western Europe; CHS	40–65 y ≥30 pack-years	Test: 1 y. CS: 0.824; FS: 0.830; ES: 0.843 5 y. CS: 0.767; FS: 0.715; ES: 0.787		Limited range of predictors Needs external validation in other populations
Pittsburgh predictor[102]	Pittsburgh, USA; CHS; n = 57,096	50–79 y CS/FS; strong smoking history	0.678	Pittsburgh, USA. 0.701	Relatively simple model; lower accuracy of prediction. Derived/validated in pre-selected high-risk populations (not representative of general population of people who smoke)
LCRAT/ LDCRAT[103]	USA: CHS; n = 154,901	55–74 y	0.70–0.80		Included Hispanic, Asian and Black (non-Hispanic) people
Biobank[104]	UK: CHS; n = 502,321	37–73 y	Development: 0.84 Test: 0.83		First model to use lung function (no increase in predictive ability). People who had never smoked inflated AUC
HUNT[105]	Norway n = 65,237	>20 y		0.87	Developed/tested in patients with wide range of smoking exposure and ages, including ~30 year-olds, who are at low risk (may have inflated AUC)

[a]Frequently reported and assessed plus recently developed risk prediction models, with potential to identify high-risk individuals for lung cancer screening.
[b]Emphasis on enrolling subsets of special interest, including minority patients, younger patients (<50 years old), and people who had never smoked during their lifetime.
AUC, area under the curve ; CS, people who currently smoke; C-CS, case-control study; CHS, cohort study; ES, people who have smoked during their lifetime; FS, people who used to smoke; GP, general population; LCRAT, lung cancer risk assessment tool; LDCRAT, lung cancer death risk assessment tool; NA, not available; NS, people who have never smoked.

Table 4B. Predictive Factors Included in Risk Prediction Models for Lung Cancer

Model		Bach[93]	Liverpool Lung Project[96]	Spitz[98]	African-American[99]	PLCO$_{m2012}$[100]	Hoggart[101]	Pittsburgh Predictor[102]	LCRAT / LDCRAT[103]	Biobank[104]	HUNT[105]
Predictive Factors	Age	✓	✓			✓		✓	✓		✓
	Sex	✓	✓						✓		
	Body mass index					✓			✓		✓
	Race/ethnicity					✓			✓		
	Socioeconomic status (education)					✓			✓		
	Smoking history/ abstinence	✓			✓	✓	✓	✓	✓	✓	✓
	Lung function test									✓	
	Recent chest X-ray										
	History of hay Fever			✓	✓						
	Family history of lung cancer		✓	✓		✓			✓		
	Personal history of cancer					✓					
	Secondary smoke exposure	✓		✓							✓
	Asbestos exposure	✓	✓	✓	✓						
	Dust exposure			✓	✓						
	Pneumonia (previous diagnosis)		✓	✓							
	Malignant tumor		✓								
	COPD			✓[a,b]	✓	✓			✓[b]		
	SNPs						✓				
	Environment[c]						✓				

[a]Prior respiratory disease.

[b]Previous diagnosis of emphysema.

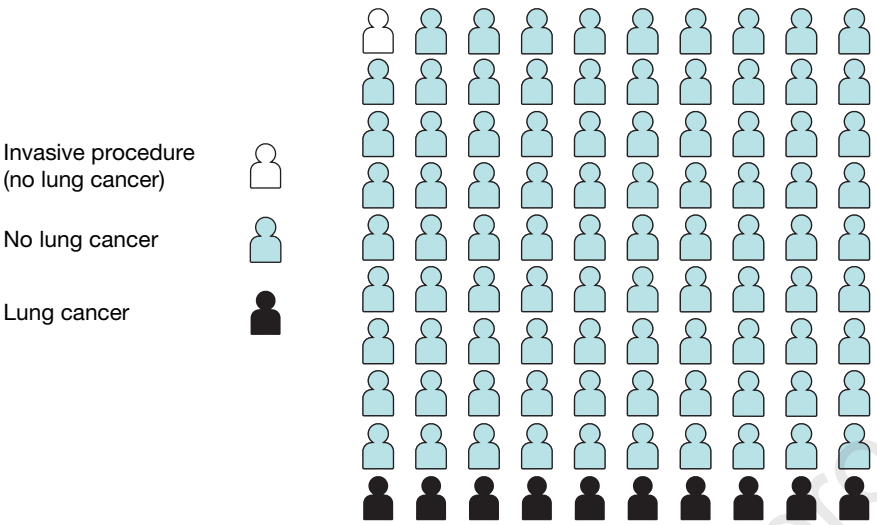
[c]10 occupational/environmental exposures previously implicated with lung cancer.

COPD, chronic obstructive pulmonary disease; LCRAT, lung cancer risk assessment tool; LDCRAT, lung cancer death risk assessment tool; SNPs, single-nucleotide polymorphisms associated with lung cancer.

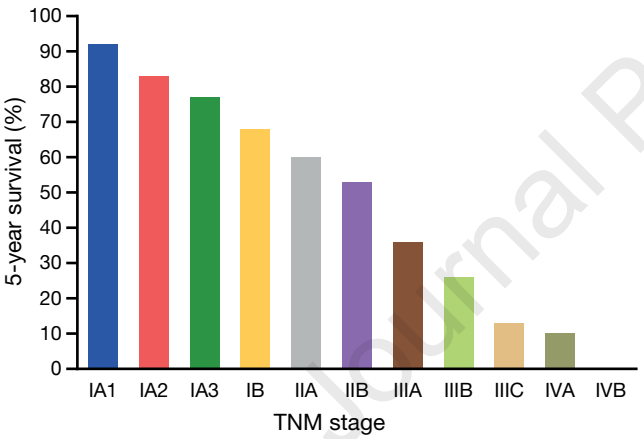
Figure 1. Updated decision aid to support shared decision-making in clinical practice. *(A)* Lung screening outcomes per 100 high-risk individuals during full duration of screening eligibility. A scan result leading to at least a recommendation for follow-up imaging occurs in about 13% of baseline scans and 6% of yearly follow-up scans.[63] *(B)* 5-year survival of all patients with lung cancer, by stage at diagnosis (not specific to screening).[64] *(C)* Overall survival of all patients with lung cancer, by clinical stage (8th edition of the TNM classification) at diagnosis (not specific to screening). Figure adapted from Goldstraw P et al. J Thorac Oncol. 2016;11(1):39-51.[64] Stage of lung cancer at diagnosis, diagnosed within *(D)* and outside of *(E)* CTLS programs. TNM, tumor, node, metastasis.

Lung Screening Shared Decision-Aid

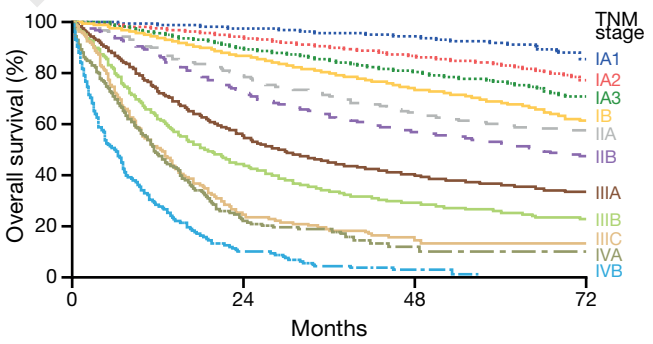
A. Lung screening outcomes over full duration of screening eligibility



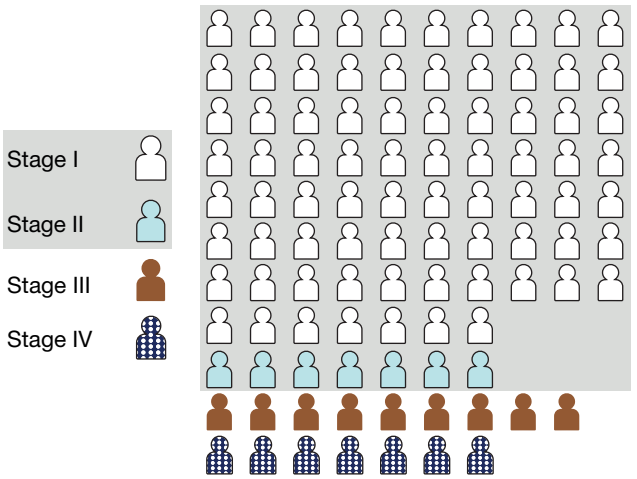
B. 5-year survival by lung cancer stage at diagnosis



C. Survival over time by lung cancer stage at diagnosis



D. Diagnosed in a lung screening program



E. Diagnosed outside of lung screening programs